Carbapenemase Producing Enterobacteriaceae - screening and contact tracing in Region Stockholm in comparison with two other Swedish regions

Degree Project in 1-year Master program in medical microbiology, with specialization in Infection Prevention and Control, 15 hp

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Abstract

Background: Carbapenemase Producing Enterobacteriaceae (CPE) is a growing problem all around the world. Sweden is relatively spared and there are very seldom outbreaks within the health care sector. Region Stockholm does contact tracing on all new and known carriers of CPE in health care institutions while other regions test only those who share room and toilet.

Aim: Is the CPE contact tracing strategy in Region Stockholm more effective in finding patients with a nosocomial spread than in Region Västra Götaland and Region Skåne who has less meticulous contact tracing strategies?

Materials and methods: Contact tracing and screening data were collected from the Karolinska University Laboratory for the years 2018 – 2020 and corresponding data were asked for from Region Västra Götaland and Region Skåne. Descriptive data were analyzed in Excel.

Results: During the study period the Karolinska University Laboratory handled 23,862 contact tracing tests. Of 288 samples from 169 patients who turned out positive for CPE in screening, bacterial culture and contact tracing altogether, 65 samples (49 patients) turned out positive from contact tracing. Four patients were traced to have the same strain as the index and were considered infected within the health care sector. Region Västra Götaland discovered 6 patients and Skåne 2 patients, respectively, who were infected within the health care sector during the same time.

Conclusions: There was an enormous number of contact tracing tests for CPE performed in Region Stockholm. Only four patients turned out to be infected within the health care sector. They would have been discovered by using the close contact tracing and screening in the same way as they do in Region Västra Götaland and Region Skåne.

Implications: Based on the findings it could be argued that it would be enough to perform contact tracing on patients who have shared the same room or toilet with a newly diagnosed CPE carrier. There seem to be no reason to test patients when a known carrier is admitted to a ward since the index will have a single room and staff will be aware of the situation.

Background

In a more and more globalized world with an excessive use of antibiotics Carbapenemase Producing Enterobacteriaceae (CPE) is increasingly becoming a big problem worldwide; not only for the healthcare systems but also for each person who has become a carrier or is infected. There are many countries in the world where CPE is endemic and in most European countries sporadic outbreaks occur (1).

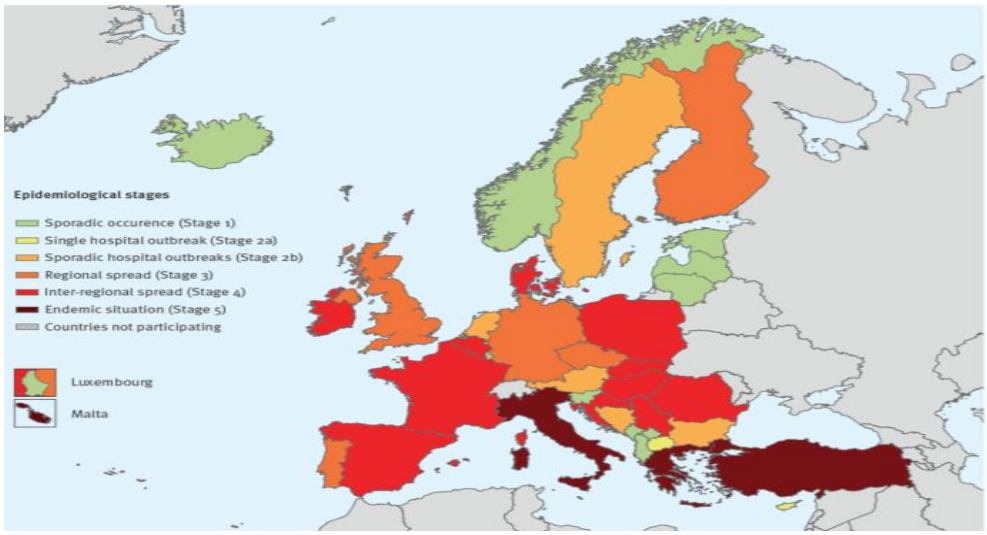

Fig. 1 Epidemiological situation of carbapenemase-producing Enterobacteriaceae, assessment by national experts in European countries, July 2018. (Fig. 1 © ECDC [2005-2021], license: CC BY 4.0.)

The situation is most serious in southern Europe especially in Greece and Italy where CPE has become endemic (Fig. 1) (2) and where about 25-50% of clinical invasive isolates of *Klebsiella pneumoniae* are resistant to carbapenems of which the majority are CPE (Fig. 2)

Fig. 2 Percentage of invasive K. pneumoniae isolates with resistance to carbapenems, EU/EEA, 2017. (Fig. 2 © ECDC [2005-2021], license: CC BY 4.0.)

In Sweden we have a restrictive antibiotic prescription policy and we are relatively spared from hospital spread of CPE (3). New cases are mainly associated with traveling abroad, are found in microbiological cultures from people from countries where CPE is endemic or in microbiological cultures from patients who have had hospital care abroad. Within the health care we want to minimize the spread of CPE between patients but how do we do this most effectively? A systematic review of articles has been performed to evaluate control measures of CPE outbreaks in hospital settings (4). Some of the important measures to prevent or in ceasing an outbreak included early detection, patient/staff cohorting, patient isolation, contact precautions such as gloves, hand disinfection and handwashing, staff education in how to prevent further spread and enhanced environmental cleaning and decontamination (1).

In Sweden, a national screening and contact tracing document for Extended Spectrum Beta-lactamase producing Enterobacteriaceae, in this context named EPE, which includes CPE, was published in 2014 by the Public Health Organization (5). The document is in terms of a more general program and the recommendation is that each region has its own guidelines. On the contrary Denmark and Norway have national screening and contact tracing programs (6, 7).

To avoid nosocomial spread of CPE in hospital settings, Region Stockholm has a meticulous screening and contact tracing program since 2012, when the carriage of or infection with CPE became notifiable. A short summary of the contact tracing part of this program will follow below. In the screening part of the program the physician usually asks for EPE on the cultivation referral, where CPE is included.

Contact tracing should be performed around patients both in the situation of newly discovered carriage while in hospital, including cases found after care abroad outside the five Nordic countries, and around known carriers at hospital admission for any reason. A carriage of CPE is considered lifelong. When a patient who is a known carrier of or has an infection with CPE is hospitalized or referred to a long-term care facility for elderly all patients in the same ward should be tested. The same procedure will apply even when the patient with CPE is a carrier only, without any risk-factors, such as diarrhea, dressing requiring wounds, urine catheter, other urine diversion, stoma bag or invasive assisted breathing. In hospital settings, samples from feces and defined risk-factors should be collected from those who are hospitalized in the same ward for more than 8 hours. Around patients with newly discovered CPE, while in

hospital, contact tracing is performed immediately and at discharge while around patients who are a known carrier of CPE and those who have been diagnosed after care abroad microbiological cultures are only performed at discharge. CPE should be specifically asked for on the cultivation referral. If a patient stays in a ward more than 2 weeks a weekly test on all patients should be performed. One week after discharge of the CPE carrier, you should investigate if there are any patients left who have been cared for, for more than 8 hours, together with the CPE patient and test them. If a new case of CPE is discovered in a long-term care facility for elderly all other patients who are cared for by the same staff should be tested immediately and later according to below. When a known carrier is admitted, testing should be performed after three months and thereafter once a year. If the CPE carrier moves or dies contact tracing should be performed on the remaining patients where after the testing can end (8).

Some regions in Sweden and in our neighboring countries, Denmark and Norway, have adopted a less meticulous contact tracing program where they work after “the stone in the pond” principle. This means that if they find a new case among the close contacts of the index patient they will investigate further. But if they do not find anyone among the close contacts, they do not test everyone in the ward. Close contacts in this context are those who have shared the same room, toilet or medical equipment.

In Region Västra Götaland the tracing program describes that all new cases and those with known CPE carriage should be judged according to the risk of spreading the bacteria. Together with the Department of Infection Prevention and Control contact tracing is performed. Their basic principle is when the patient has his/her own room and toilet no contact tracing is done. If a newly diagnosed patient has shared room and toilet usually contact tracing is performed but if the patients have no risk-factors you could refrain tracing the other patients in the room. You should consider risk-factors of both the index and fellow patients. (9).

In Region Skåne the contact tracing program describes that the patients physician/care unit is responsible for the contact tracing and should contact the Department of Infection Prevention and Control for assistance. Their basic principle is the same as in Västra Götaland which means to case trace new CPE cases but not known carriers. Contact tracing includes patients who have shared the same room or toilet as index. If the CPE carrier has risk-factors you

should also perform contact tracing on the other patients who have risk-factors and have shared the same medical equipment (10).

Since regions in Sweden do not have the same contact tracing programs for CPE, the question that came to mind was are there differences in the number of newly diagnosed hospital acquired infections of CPE and spread or outbreaks in our different regions? And what is the most effective way to use our common resources for the benefit of both patients and staff?

Aim and Research questions

The aim of this study was to evaluate the testing and contact tracing procedures for Carbapenemase Producing Enterobacteriaceae (CPE) within the health care system in Region Stockholm and to compare the result and the procedures with two other Swedish regions.

The research questions were:

- How many tests where CPE was specifically asked for (contact tracing) and how many screening tests for EPE were performed during 2018 – 2020?
- Does Region Stockholm find more new cases of CPE through contact tracing compared to Region Västra Götaland and Region Skåne, the second and third largest regions-who have less meticulous contact tracing programs?
- How many of the positive tests were due to a spread within the health care system and was found through contact tracing?
- Those infected within the health care sector, where and when had they been infected?

Materials and Methods

There are three microbiological laboratories in Region Stockholm. These are the Karolinska University Laboratory, Unilabs and the SYNLAB Group (former Aleris). In the laboratory, culture plates with antibiotics that inhibit growth of EPE but not CPE are used to detect CPE only. All cultivation results where CPE was specifically asked for and all cultivation results where screening for EPE was performed were collected from the Karolinska University Laboratory. Tests from all care givers who sent the specimens to the Karolinska University Laboratory were included in the data. From Unilabs and the SYNLAB Group only data from test results where CPE was asked for was possible to collect. Data of the total number of annually new diagnosed cases of CPE, cases found due to healthcare spread and the number

of cultures performed to find them were asked from Region Västra Götaland and Region Skåne. The study period was from 2018- 2020.

Positive cultivation results for CPE were analyzed to investigate the test indication and especially if the patients were infected within the health care sector so called nosocomial infection. Data for each positive CPE case that was registered during 2018 – 2020 was analyzed in the epidemiological database called NYSA which is a tool used in the everyday work at the Department of Infection Prevention and Control in Region Stockholm and facilitates contact tracing of notifiable resistant bacteria. Positive test results where CPE was asked for were also controlled in the national database SMINET for information from the reporting doctor. In Sweden all notifiable infectious diseases are reported in SMINET.

In this register study we have used descriptive data to address the research questions. Data, tables and figures were performed in Excel. Screening and contact tracing programs from Region Västra Götaland, Region Skåne were compared to the one in Region Stockholm. Data of the total number of cases and those with nosocomial spread of CPE were compared between the regions. Fisher's Exact Test, Exact Significance (2-sided), was used to evaluate the differences in nosocomial spread of CPE between the three regions and was performed in SPSS. P-value below 0.05 was considered significant.

Ethics

There were some ethical considerations during the planning of the study question. To evaluate the screening and case-tracing procedures within Region Stockholm meant that data from the microbiological laboratories and the epidemiological databases, where full identification of the patients needed to be revealed and processed. But all positive cases of CPE both from screening and case-tracing are fully accessible from the epidemiological data base (NYSA) that is used every day at the Department of Infection Prevention and Control. Since a misuse could appear anytime if data would be handled in a careless way our position was that when a study was done on data that we have full access to every day we would be even more thorough not to reveal any personal information from any patients. The data was strictly anonymous and used in a descriptive way. That was why we did not consider that an approval from the ethics review authority was necessary and we were satisfied with the approval from the Head of Department of Infection Prevention and Control.

Results

Reported new cases in the local database NYSA for Carbapenemase Producing Enterobacteriaceae (CPE) in Region Stockholm were 59 (2018), 75 (2019) and 43 (2020). About half of the patients in 2018 and 2019 were detected due to hospital care abroad, while there was a decrease to about a third in 2020.

Since screening for Extended Spectrum Beta-lactamase producing Enterobacteriaceae (EPE) also detects CPE, the specific CPE cultivation referral is almost always used by the clinicians for contact tracing. It is meant to be used precisely as a test when you want to know if another patient has been infected by the index patient. That was the basic understanding of the test that we have used in this study. When the clinicians ask for EPE it is most often a screening procedure. Some clinicians specifically might ask for CPE on the cultivation referral when a patient has been hospitalized abroad, but most often screening for EPE is demanded in that situation. In this study we interpreted CPE cultivation as contact tracing tests and EPE cultivation as screening tests.

Number of cultures for Carbapenemase-producing Enterobacteriaceae and Extended Spectrum Beta-lactamase producing Enterobacteriaceae in Region Stockholm

During the study period (2018 – 2020) the Karolinska University Laboratory handled 43,058 samples among 31,912 patients which were either a screening test to look for EPE or tests where you ask specifically for CPE most often due to contact tracing. The group where CPE was asked for was slightly larger with 23,862 (55%) samples from 16,933 (53%) patients. The EPE-screening group had 19,196 (45%) of the samples from 14,979 (47%) patients. Some patients were tested with both an EPE screening test and a CPE contact tracing test and these patients end up in both groups. The samples which were positive for CPE in the CPE contact tracing referrals were 0.27% while the patients who turned out positive were 0.29% (Table 1). The patients who turned out positive in the CPE tracing test will be described later in the result section.

Table 1. Number of bacterial cultures for *Extended Spectrum Beta-lactamase producing Enterobacteriaceae* (EPE) and *Carbapenemase-producing Enterobacteriaceae* (CPE) and number of positive results for *Carbapenemase-producing Enterobacteriaceae* cultures and patients performed at the Karolinska University Laboratory 2018 – 2020

	2018	2019	2020	Total
Total number of samples	14,676	15,806	12,576	43,058
Total number of patients	10,771	11,644	9,497	31,912
EPE screening samples	7,522	6,631	5,043	19,196
Patients EPE screening	5,718	5,353	3,908	14,979
Samples positive for CPE	37	61	15	113
Patients positive for CPE	30	48	11	89
CPE tracing samples	7,154	9,175	7,533	23,862
Patients CPE tracing	5,053	6,291	5,589	16,933
Samples positive for CPE	13	30	22	65
Patients positive for CPE	10	25	14	49

The second largest laboratory in Stockholm, Unilabs handled approximately 11% of the CPE tracing samples, 2,615 compared to the Karolinska University Laboratory, whereof seven were positive for CPE. The SYNLAB group had done 46 CPE contact tracing tests during 2018 – 2020 and one was positive for CPE. None of these eight cases were due to a health care spread. As we were not able to collect data of the EPE screening cultivation results from these two laboratories, data presented for Region Stockholm in this study come from the Karolinska University Laboratory as they have responded and supplied well documented and thorough data. As they perform approximately 90% of all microbiological diagnostics our assumption was that this will give a comprehensive picture of the situation in Region Stockholm.

Referral departments and number of cultures for Carbapenemase-producing Enterobacteriaceae and Extended Spectrum Beta-lactamase producing Enterobacteriaceae performed at the Karolinska University Laboratory

The case-tracing cultivations where CPE was asked for during 2018 – 2020 were distributed as follows. Larger hospitals did between 84 – 89% of the testing, while long-term care facilities for elderly accounted for 0.5 – 1% of the testing and other care facilities accounted for 10.5 – 15% of the testing (Fig. 3). The larger hospitals include Karolinska University Hospital in Solna and Huddinge, Danderyd Hospital, South Hospital (Södersjukhuset), Capio S:t Görans Hospital and Södertälje Hospital. Other care facilities include for example external

geriatric clinics, private clinics and dialysis outward clinics. Screening samples for EPE during the same period and from the same caregivers were as follows. The hospitals had a range between 91 – 94%, long-term care facilities for elderly between 1 – 2% while other care facilities had a range between 4 – 7% (Fig. 3).

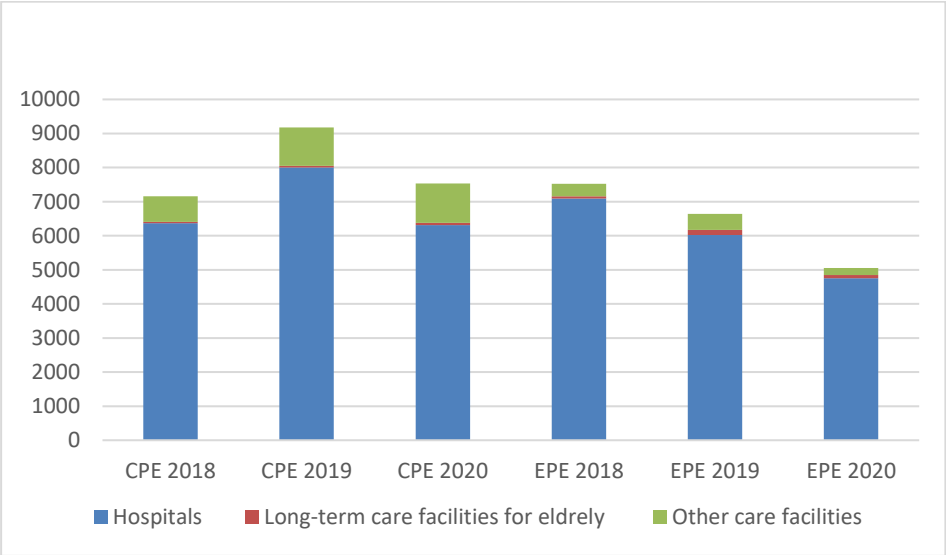

Fig. 3 Number of bacterial cultures for *Carbapenemase-producing Enterobacteriaceae (CPE)* and *Extended Spectrum Beta-lactamase producing* Enterobacteriaceae *(EPE)* performed *at the Karolinska University Laboratory divided into different health care categories*

Some wards perform screening of notifiable resistant bacteria, including EPE according to special routines because of vulnerable patients. The Intensive Care Units (ICU) and the Departments of Neonatology accounted for 46% of all screening tests 2018, 34% 2019 and 52% in 2020 (Fig. 4).

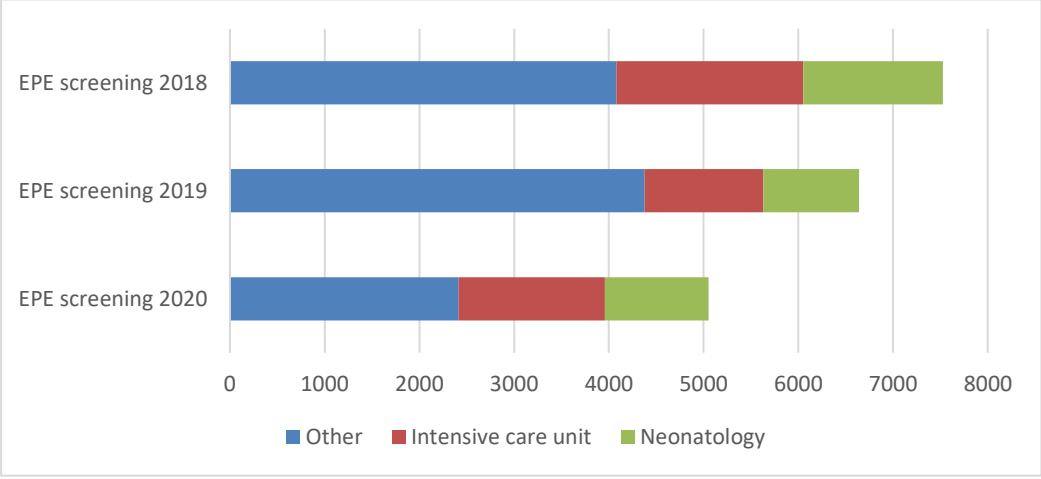

Fig. 4 The number of Extended Spectrum Beta-lactamase producing Enterobacteriaceae (EPE)*-screening tests from Intensive care units, Departments of Neonatology and all other health care units in Region Stockholm*

Comparison of statistics for Carbapenemase-producing Enterobacteriaceae between three Swedish regions

Stockholm, the largest region in Sweden had an approximal population of 2.4 million inhabitants and had 177 CPE cases during 2018 – 2020. In four cases microbiological cultures could conclude that a nosocomial spread had occurred. That was 2.3% of the patients. The second largest region, Västra Götaland, with an approximal population of 1.7 million inhabitants had 80 cases during the same period. They found six cases through laboratory findings where a nosocomial spread was confirmed. That was 7.5% of the patients. Region Skåne, the smallest region among the three had an approximal population of 1.4 million inhabitants. They found 55 CPE cases and for two of them laboratory findings confirmed that a nosocomial spread had been done. That was 3.6% of the cases (Fig. 5). We were not able to receive the total number of cultures for EPE and CPE performed in Region Västra Götaland and Region Skåne during the study period.

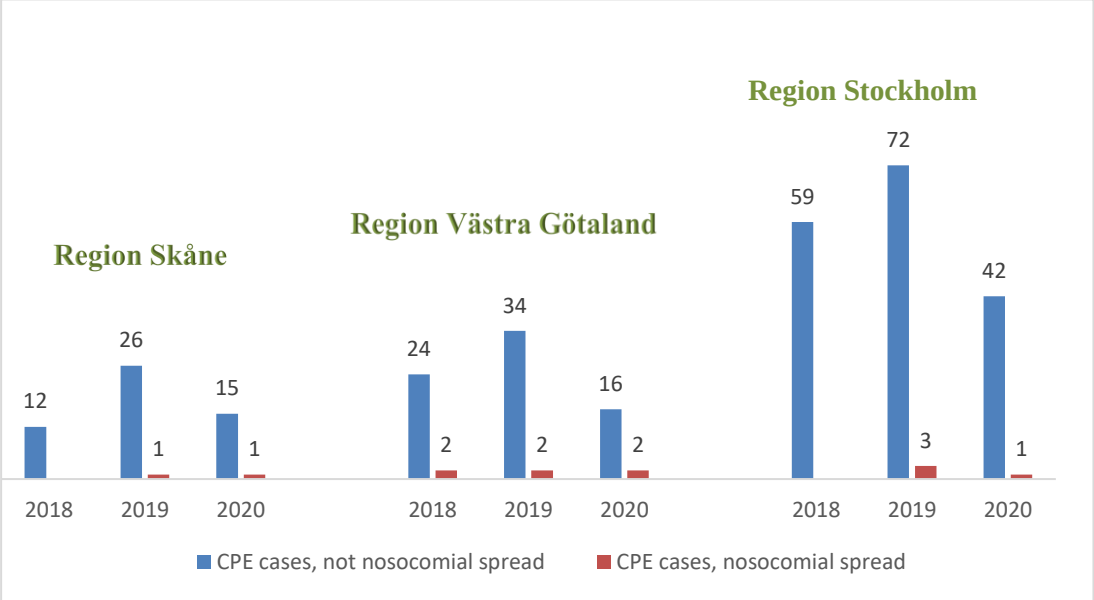

Fig. 5 Annually diagnosed Carbapenemase-producing Enterobacteriaceae (CPE) cases divided in cases with nosocomial spread and without nosocomial spread within the health care sector in the three largest regions in Sweden between 2018 - 2020

The number of nosocomial CPE cases among the total amount of CPE cases per region was compared between the regions. P-value: Stockholm (n=4/177) vs Västra Götaland (n=6/80) = 0.075; Stockholm (n=4/177) vs Skåne (n=2/55) = 0.629; Västra Götaland (n=6/80) vs Skåne (n=2/55) = 0.472. The average incidence of CPE cases per year was highest in Region Stockholm with 2.5/100 000 while Region Västra Götaland had an incidence of 1.6/100 000 and Region Skåne had 1.3/100 000.

Cultures positive for Carbapenemase-producing Enterobacteriaceae performed at the Karolinska University Laboratory

The Karolinska University Laboratory cultivated 288 samples from 169 patients with a positive result for CPE during 2018 – 2020. There were 183 (63.5%) samples that originated from male patients and 105 (36.5%) samples from female patients. Percentual more samples were taken from male patients. The sex distribution among the 169 patients were 96 men (57%) and 73 women (43%). The male patient samples dominate in all categories except for clinical bacterial cultures in samples from urine. In the CPE screening/contact tracing category, for an example, positive samples from male patients were 49 compared to 16 for females. Divided into categories in numerical order: (Fig. 6)

1. EPE screening; 113 (89 patients)
2. Bacterial culture due to clinical symptoms; 110 (31 patients)
3. CPE screening/contact tracing; 65 (49 patients)

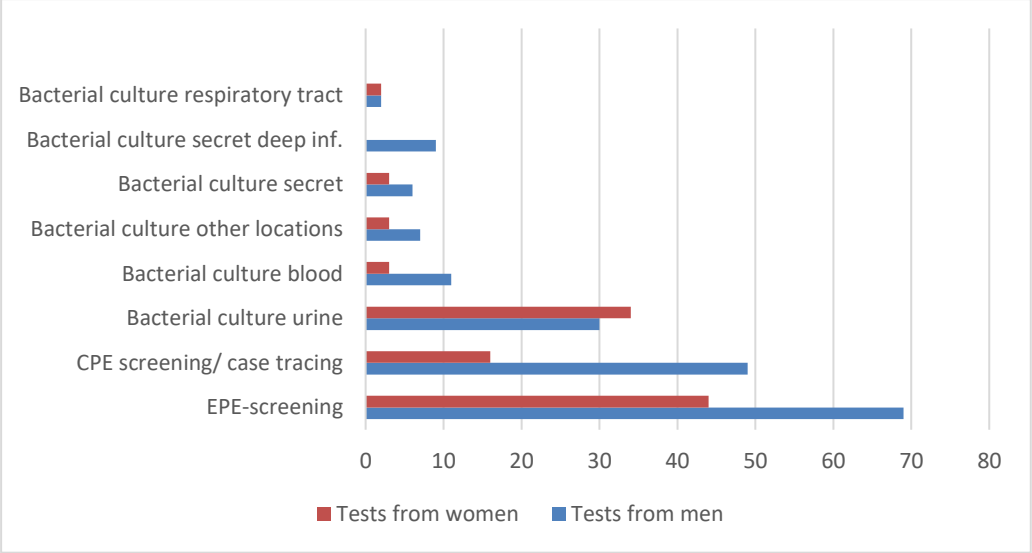

Fig. 6 All positive cultures for Carbapenemase-producing Enterobacteriaceae (CPE) during 2018 – 2020 from the Karolinska University Laboratory (N=288). Found through bacterial cultures, CPE contact tracing or Extended Spectrum Beta-lactamase producing Enterobacteriaceae (EPE)*-screening. Divided into sex whereof 96 were men and 73 women (N=169)*

The age distribution from the 169 patients is displayed in figure 7. There was a peak among the very young children, many of whom were found in the first year of life. Then we saw the largest peak among the age-group 65 to 79 with an excessive proportion among men before there was a decline among the elderly.

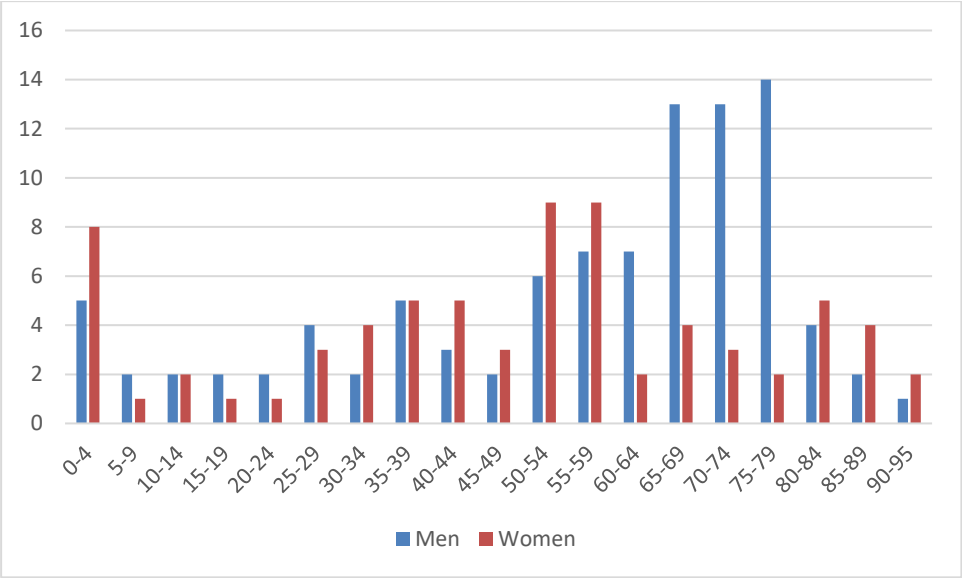

Fig. 7 All positive patients for Carbapenemase-producing Enterobacteriaceae (CPE) during 2018 – 2020 from the Karolinska University Laboratory divided into sex and age groups with 5-year intervals (N=169)

Positive tests where Carbapenemase-producing Enterobacteriaceae was specially asked for performed at the Karolinska University Laboratory

Before the covid-19 pandemic the most common cause to find CPE, in tests where you ask specifically for CPE, was in screening due to hospitalization abroad. The figures in 2018 and 2019 were eight and 18 respectively but went down to three in 2020. Contact tracing where you "accidentally" find a new CPE carrier with another strain was the most common cause during 2020. Of the 49 patients with positive CPE culture (65 samples) where the clinician asked for CPE, 14 patients were diagnosed in contact tracing. Of these, only four patients with the same strain as the index patient were found, while 10 patients had another strain. On the remaining 35 patients the cultures performed were screening tests concerning hospital care abroad, 29 patients and patients from highly endemic countries, six patients (Fig. 8)

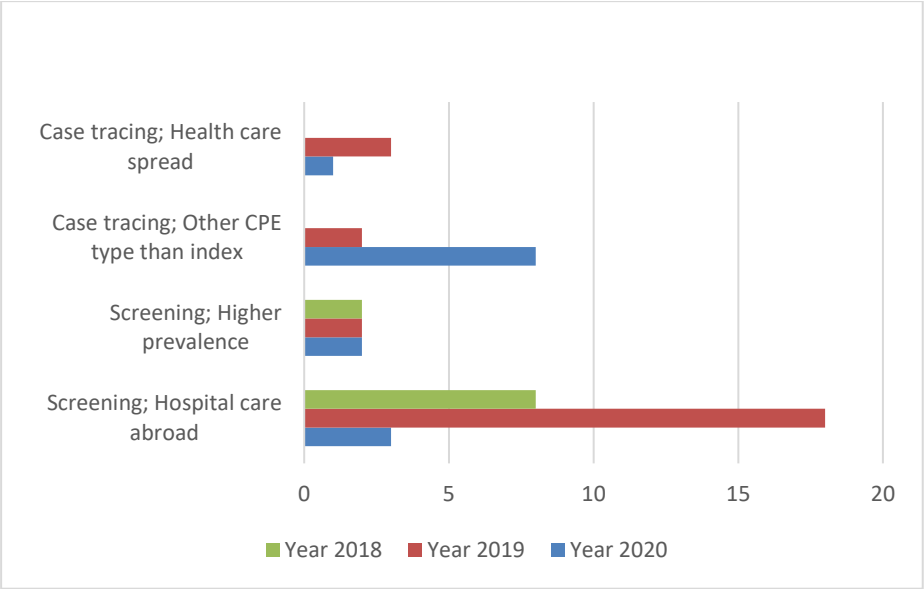

Fig. 8 Physicians indications for testing for Carbapenemase-producing Enterobacteriaceae (CPE) per year and number of positive patients diagnosed at the Karolinska University Laboratory

Positive contact tracing contacts in the health care sector

The four occasions where a health care spread had been documented (Fig. 5 and 8) were as follows: Two children at the Department of Neonatology became carriers of the same CPE strain from a third child during care in incubators in the same ICU room. One woman became carrier of the same strain as her fellow neighbor at their long-term care facility for elderly. The neighbor suffered from dementia and liked to go into her fellow patients' rooms. One patient became a carrier with the same strain as a fellow patient at the Department of Infectious diseases at one of the hospitals in Stockholm. They had neighboring rooms.

Discussion

The aim of this study was to evaluate the contact tracing program for Carbapenemase Producing Enterobacteriaceae (CPE) in Region Stockholm. There are different ways that countries and regions perform screening and contact tracing in order to control CPE and avoid people from catching CPE (4). We should take hospital infections and outbreaks with CPE highly serious because there is an increased risk of mortality among vulnerable patients catching CPE but luckily we see very few outbreaks with CPE in low incidence countries (11). There was nothing that indicated that contact tracing for CPE was more effective in Region Stockholm than in the two other large regions in Sweden where a less meticulous contact tracing strategy was adopted. At least three of the four cases found through contact tracing would have been detected by the close contact strategy or the screening strategy used

within wards with vulnerable patients like ICUs and wards at the Department of Neonatology etc. The fourth case could maybe have been undetected if a less meticulous contact tracing strategy would have been applied. The two patients had separate rooms with their own toilet. On the other hand, the index patient had risk-factors so an extended contact tracing could most likely have been imposed by the physician.

Of the 23,862 contact tracing tests 65, 49 patients, turned out positive for CPE. Of these positive tests we could conclude that a very small proportion, only four patients, had been infected within the health care sector. Ten of the patients were found through contact tracing but had another strain of CPE and were not connected. The largest number of positive results, 29 patients, are from the group of patients who had health care abroad within six months before they were admitted to one of the hospitals in Region Stockholm. These findings should have been detected if the physician would have followed the screening and contact tracing program and had performed an EPE screening. This indicates that some physicians use the CPE contact tracing test as a screening test.

One of the examples above where contact tracing caused accidental detection of new CPE cases occurred in a ward at the Department of Surgery in Södertälje Hospital. They took care of a patient who was a carrier of CPE and was admitted for a long period during which 659 contact tracing tests were performed. They found three positive CPE patients but none with neither the same strain as the index patient nor the same strain among the new cases. It was time consuming for the staff, expensive and inconvenient for all patients who had to be tested.

Of the 19,196 Extended Spectrum Beta-lactamase producing Enterobacteriaceae (EPE) screening tests 113 (89 patients) turned out positive for CPE. A higher proportion of the EPE screening tests were performed at the larger hospitals (91 – 94%) where there are several ICUs and emergency wards for patients who recently have been hospitalized abroad. EPE-screening tests were seldom done in other care facilities, but CPE contact tracing was more frequent, 10 – 15%. This could reflect where you find the CPE carriers for instance in geriatric clinics where many tests must be performed around a known CPE carrier. The long-term care facility for elderly had a small proportion in both groups with around 1% of the tests which could raise the question if the long-term care facilities for the elderly indeed do follow the screening and contact tracing program? Most people living in long-term care facilities for elderly nowadays are older than 80 years. The part of positive CPE patients in that age group was 11% of the total number (18 out of 169). EPE screening after recent

hospitalization abroad is very rare in this group for natural reasons. This could indicate that CPE is still quite uncommon among elderly Swedes.

The reason why Region Stockholm had the highest incidence of CPE cases per year could be due to different causes. According to the Statistics Sweden, Region Stockholm has a population of 11.6% with a foreign background outside of Scandinavia while Region Västra Götaland has 8.5% and Region Skåne has 9.7% (12). A greater population with a foreign background could lead to more travel and more exposure for healthcare in other countries. One cause could be that the fecal flora you get as an infant most often will persist in adulthood. Also what medication, antibiotics and food you have been exposed to during life will matter which means that if you were born in a highly endemic country the risk will be higher that you are a carrier of CPE (13). In this aspect of ethnicity, data showed that among the 177 newly diagnosed CPE cases during these three years many had a foreign name and the incidence could reflect the incidence from their home country. Another reason of the higher incidence in Region Stockholm could be that more carriers of CPE were "accidently" found in the extensive contact tracing strategy and would go undetected in the other two regions.

The higher level of nosocomial spread of CPE in Region Västra Götaland (7.5%) compared to Region Skåne (3.6%) and Region Stockholm (2.3%) seems to be quite large at a first glance. However, the figures are too small in all the regions both concerning the total number of CPE cases and those with a hospital acquired infection to make any conclusions in this regard. Statistical analysis with Fisher's Exact Test the P-value between Stockholm versus Västra Götaland was 0.075. Even if the figure is quite low it is still not significant. This emphasizes our assumption that the figures are too small to draw any conclusions and could be due to coincidence.

It is encouraging that we saw very few nosocomial spreads during these three years from three regions that constitute 5.5 million inhabitants together. One question to pose in this context would be: Is it relevant to find all fecal carriers of notifiable resistant bacteria in patients who do not have any risk-factors? If there are many inward patients who are undetected carriers of CPE what are the consequences if they do not have risk-factors neither for higher risk of becoming a carrier of CPE nor for spreading CPE? Severe invasive clinical infections are rare both for those caused by carbapenemase producing *Klebsiella pneumoniae* as for carbapenemase producing *E-coli*, which is a more frequent agent of CPE in Sweden (14). Of less severe infections in this study the majority were urinary tract infections, but the

number during the three years was low, only 45 patients. Furthermore, there are studies that have examined the psychological effects in patients after receiving the information that you have become a carrier of a notifiable resistant bacterium. The mere knowledge could be a huge stress for many patients (15, 16). Also the staff can have a hard time handling with psychological stress when they care for patients with a resistant bacterium (17). The contact tracing program among patients with methicillin resistant staphylococcus aureus (MRSA) in Region Stockholm has developed from contact tracing all patients to focus more on the risk-factors (18). The equivalent could be emphasized in the contact tracing among CPE patients.

A fear was that the low number of CPE cases in 2020 were due to a decline in testing procedures because of the stress the covid-19 pandemic has had on the health care. There was indeed a decline in case-tracing tests 2020 compared to 2019 but there were more tests performed in 2020 compared to 2018. If there had been no pandemic the CPE cases would most likely have continued to increase but was halted due to all restrictions around the world and the cease of traveling with a possible need of hospitalization abroad which is one of the most common causes for catching CPE. However, it seems as though the case-tracing continued in an unreduced rate and instead there was a decline in EPE screening tests due to the above-mentioned cease of traveling abroad. The emphasizing on distancing and handwashing has meant that nearly all viral outbreaks both in the community and in the health care sector, except covid-19, has vanished. For an example the figures for the seasonal influenza were on an extremely low level (19). Could this also have caused a decrease of CPE cases in 2020?

Why there is a minor male dominance (57%) among all positive CPE cases during the study period is hard to have any evident reason for. Men had a higher risk of contracting CPE except for urinary tract infections. Women contract urinary tract infections more often than men and that was probably the reason why CPE was found with a higher frequency in clinical bacterial cultures of urine in female samples (20).

If you anyway want to have a more thorough contact tracing schedule than just looking at the close contacts who share the same room, then one option is to differentiate the patient risk-factors for spreading the bacteria. Patients who suffer from diarrhea or are confused and pose a risk of getting close to other patients are more likely to spread their fecal flora. In a study from an outbreak of carbapenemase producing *Klebsiella pneumoniae* the research showed that many of the patients had a natural decolonization after 6 months (21). This would imply

that the longer a patient without any risk factors has been a carrier of CPE the less likely it would be that he or she will spread CPE.

Emphasizing on good hygienic control measures both when you know if there is a CPE carrier or not is the way to go. More and more hospitals both larger and smaller build single rooms when they build new hospitals and when they reconstruct old hospital buildings to minimize the risk of infection (22). This and good hygienic possibilities for the staff are two important things to keep the spread of all microorganisms, resistant or not, within the health care settings on a very low level (23). We can never come down to zero contact tracing infections even if that is our goal. There will always be single staff or patients that miscalculate a situation and by mistake forwards a resistant bacterium to other patients.

When a patient who is a known carrier of CPE is admitted to a hospital there are several things that will take place: Single room with your own toilet, staff who attend to the patient will not handle food in the kitchen and if the patient has a risk factor then cohort is emphasized. Staff will be aware of the CPE patient and will be extra thorough with hand hygiene and cleaning in the room. The risk of a spread is minimized from the beginning with actions similar to those when there is a spread within a hospital (24). The time and cost benefits from scaling down the CPE tracing procedures could be invested in education to maintain and emphasize on basic hygiene, so the slim risk of a hospital spread is even more minimized.

One weakness in the study was the difficulty to get the exact number of and the right indication for culture referrals for CPE without going through all the thousands of referrals with a negative result. Our assumption was that cultures performed where CPE was especially asked for, 23,862 tests, were contact tracing tests, which is the most probable interpretation. Screening for CPE per se is seldom performed at all but is included in culture referrals for EPE screening. Another weakness was that we were not able to get the result of the number of cultures from the other two regions during the study period. As they do not perform contact tracing around known CPE carriers, we presumed that the amount of tests would be much fewer than in region Stockholm.

Our hope is that this study will lead to an effective way to perform contact tracing of CPE within Region Stockholm. To minimize the tests to an adequate level is important so the staff has more time to concentrate on the care of the patients. It would lead to a cost benefit for

each ward who has the financial responsibility when they have a CPE carrier admitted. The patients inconvenience of taking a feces sample would also be avoided.

Conclusions and Implications

Our recommendation would be that Region Stockholm will adopt the contact tracing programs of CPE from Region Västra Götaland and Region Skåne and follow their principles of proportionality. That means to start contact tracing those who have shared the same room, toilet, medical equipment or have risk factors for spreading CPE. A national program for CPE in Sweden, just like the ones in Denmark and Norway is something we think the Departments of Infection Prevention and Control should consider together with the Public Health Organization. The screening programs for EPE are probably very similar in all regions but a nationwide consensus how to perform CPE contact tracing could be important.

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References

1. European Centre for Disease Prevention and Control. Carbapenem-resistant Enterobacteriaceae - second update Stockholm: European Centre for Disease Prevention and Control; 2019 [cited 2021 April 15]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/carbapenem-resistant-enterobacteriaceae-risk-assessment-rev-2.pdf.

2. Logan LK, Weinstein RA. The Epidemiology of Carbapenem-Resistant Enterobacteriaceae: The Impact and Evolution of a Global Menace. J Infect Dis. 2017;215(suppl_1):S28-S36.

3. Ministry of Health and Social Affairs. Swedish Strategy to Combat Antibiotic Resistance 2020 - 2023: Government Offices of Sweden; 2020 [cited 2021 May 18]. Available from: https://strama.se/wp-content/uploads/2021/03/amr_strategi_eng_web.pdf.

4. French CE, Coope C, Conway L, Higgins JP, McCulloch J, Okoli G, et al. Control of carbapenemase-producing Enterobacteriaceae outbreaks in acute settings: an evidence review. J Hosp Infect. 2017;95(1):3-45.

5. Folkhälsomyndigheten. ESBL - producerande tarmbakterier Stockholm: Folkhälsomyndigheten; 2014 [cited 2021 May 14]. Available from: https://www.folkhalsomyndigheten.se/contentassets/f4df42e7e643414ba3499a9ee1801915/esbl-producerande-tarmbakterier.pdf.

6. Sundhedsstyrelsen. Vejledning om forebyggelse af spredning af CPO [Guidance on preventing the spread of CPO] 2018 [cited 2021 April 6]. Available from: https://www.sst.dk/-/media/Udgivelser/2018/CPO/Vejledning-om-forebyggelse-af-spredning-af-CPO.ashx.

7. Folkhelseinstitutet. ESBL-holdige gramnegative stavbakterier - smitteverntiltak i helseinstitusjoner OSLO: Folkhelseinstitutet; 2015 [cited 2021 April 15]. Available from: https://www.fhi.no/sv/forebygging-i-helsetjenesten/smittevern-i-institusjoner/tiltak/esbl-holdige-gramnegative-stavbakte/.

8. Region Stockholm. Handlingsprogram för MRSA, VRE, ESBLcarba- och ESBL-bildande Enterobacteriaceae Stockholm: Region Stockholm; 2019 [cited 2021 April 15]. Available from: https://vardgivarguiden.se/globalassets/kunskapsstod/smittskydd/arb/handlingsprogram.pdf.

9. Department for infection control and Hospital hygiene in Västra Götaland. Smittspårning vid multiresistenta bakterier (MRB). Västra Götaland: Department for infection control and Hospital hygiene; 2020 [cited 2021 April 14].

10. Department for infection control and Hospital hygiene in Skåne. Praktisk handläggning vid smittspårning av MRB inneliggande vård och avancerad poliklinisk behandling. Skåne: Department for infection control and Hospital hygiene; 2019 [cited 2021 April 14].

11. Segagni Lusignani L, Presterl E, Zatorska B, Van den Nest M, Diab-Elschahawi M. Infection control and risk factors for acquisition of carbapenemase-producing enterobacteriaceae. A 5 year (2011-2016) case-control study. Antimicrob Resist Infect Control. 2020;9(1):18.

12. Statistiska Centralbyrån. Befolkningsstatistik Solna: Statistiska centralbyrån; 2021 [cited 2021 April 20]. Available from: http://www.scb.se/be0101.

13. Actis GC. The gut microbiome. Inflamm Allergy Drug Targets. 2014;13(4):217-23.

14. Folkhälsomyndigheten. Extended Spectrum Beta-Lactamase (ESBL) Stockholm: Folkhälsomyndigheten; 2018 [cited 2021 May 14]. Available from: https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistik-a-o/sjukdomsstatistik/extended-spectrum-beta-lactamase-esbl/.

15. Wiklund S, Örtqvist Å, Berlin A, Stamm C, Broliden K. Experiences and consequences of living with extended-spectrum β-lactamase-producing bacteria: A qualitative study. Am J Infect Control. 2018;46(12):1394-9.

16. Andersson H, Lindholm C, Fossum B. MRSA--global threat and personal disaster: patients' experiences. Int Nurs Rev. 2011;58(1):47-53.

17. Andersson H, Andreassen Gleissman S, Lindholm C, Fossum B. Experiences of nursing staff caring for patients with methicillin-resistant Staphylococcus aureus. Int Nurs Rev. 2016;63(2):233-41.

18. Rose-Marie L. MRSA projekt- Följsamhet till gällande handlingsprogram för MRSA inom slutenvård vid Karolinska Universitetssjuhuset under perioden 1 april - 31 december 2013. Stockholm: Vårdhygien; 2015 2015-05-04.

19. Folkhälsomyndigheten. Influensarapport vecka 13-14, säsongen 2020 - 2021 Stockholm: Folkhälsomyndigheten; 2021 [cited 2021 May 3]. Available from: https://www.folkhalsomyndigheten.se/folkhalsorapportering-statistik/statistik-a-o/sjukdomsstatistik/influensa-veckorapporter/arkiv-20202021/influensarapport-vecka-13-14/.

20. Harrington RD, Hooton TM. Urinary tract infection risk factors and gender. J Gend Specif Med. 2000;3(8):27-34.

21. Lübbert C, Lippmann N, Busch T, Kaisers UX, Ducomble T, Eckmanns T, et al. Long-term carriage of Klebsiella pneumoniae carbapenemase-2-producing K pneumoniae after a large single-center outbreak in Germany. Am J Infect Control. 2014;42(4):376-80.

22. King MF, Noakes CJ, Sleigh PA. Modeling environmental contamination in hospital single- and four-bed rooms. Indoor Air. 2015;25(6):694-707.

23. Cheng VC, Tai JW, Chan WM, Lau EH, Chan JF, To KK, et al. Sequential introduction of single room isolation and hand hygiene campaign in the control of methicillin-resistant Staphylococcus aureus in intensive care unit. BMC Infect Dis. 2010;10:263.

24. Coope CM, Verlander NQ, Schneider A, Hopkins S, Welfare W, Johnson AP, et al. An evaluation of a toolkit for the early detection, management, and control of carbapenemase-producing Enterobacteriaceae: a survey of acute hospital trusts in England. J Hosp Infect. 2018;99(4):381-9.